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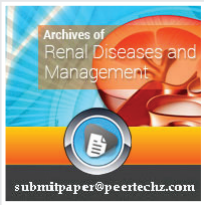

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Review Article

Gut microbiota alteration in CKD: From toxicity mechanisms to supplementation

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Abstract

Chronic Kidney Disease (CKD) refers to progressive and irreversible kidney function loss; it is currently an important health problem due to its high social costs. Decreased Glomerular Filtration Rate (GFR) causes accumulation of Uremic Toxins (UT) that must be excreted by the kidney, increasing their serum concentrations, toxicity, and hence disease progression. Dysbiosis is the alteration in the composition and structure of the intestinal microbiota and is related to systemic inflammation. Patients with CKD present biochemical changes at the intestinal level that cause dysbiosis, altering the kidney-gut axis, which is implicated in the higher production of UT. Evidence suggests an association between UT and cardiovascular risk in CKD, and different mechanisms are involved in each of them. Modulation of the gut microbiota by specific nutrients is a new strategy for the nutritional approach to CKD. Novel strategies based on the use of probiotics and prebiotics aim to reduce the synthesis and accumulation of UTs to reduce disease progression; however, with current evidence, the effect and benefit of supplementation cannot be concluded, so more research in humans is needed to identify useful bacterial strains and doses to obtain beneficial effects in CKD patients.

Introduction

Chronic Kidney Disease (CKD) is the progressive and irreversible renal function failure; with a subclinical debut, in most cases the diagnosis is tardy, conferring a poor prognosis to patients [1-3]. Actually, is considered a public health problem due to the high social costs [1,4,5]. Literature reports that behavioral interventions are fundamental pillars to prevent the progression of the disease [6].

A kidney function is the excretion of Uremic Toxins (UT), by two mechanisms: one, by glomerular filtration, and the other by transporter-mediated tubular secretion; in CKD, decreased Glomerular Filtration Rate (GFR) leads to the accumulation of Uremic Retention Molecules (URMs) [7,8], resulting in the accumulation of UTs and increase in serum concentrations, thus contributing to the characteristic uremic syndrome [6,7,9].

In CKD there is an accumulation of UT produced by gut microbial metabolism of aromatic amino acids: tyrosine, phenylalanine, and tryptophan [6,7,10], evidence *in vitro* and *in vivo* shows that these UT are implicated in pathophysiological mechanisms of cardiovascular disease, the leading cause of death in renal failure patients [5,11-14]. This review presents an overview of gut microbiota alterations in CKD, the mechanisms underlying the main UT on disease progression and cardiovascular risk, and the nutritional strategies for these conditions.

Gut microbiota

The human gut microbiota is the community of more than 100 trillion microbial cells and more than 1000 species of bacteria that coexist in the host; in non-pathological conditions, the intestinal microbiota is mainly composed of *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Verrucomicrobia* and, to a

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lesser extent, *Proteobacteria*; being Gram-negative *Bacteroidetes* and Gram-positive *Firmicutes* the most abundant [6,15].

The gut microbiota plays an essential role in the digestion of food and the metabolism of nutrients; also, it regulates the function of the immune system through the maintenance of epithelial homeostasis [6,15-17]; in addition, some microorganisms are involved in the synthesis of B vitamins, vitamin K and ascorbic acid, and the synthesis of Short-Chain Fatty Acids (SCFA) that participate in anti-inflammatory and antiproliferative mechanisms [2,6].

Diet is an environmental factor that modifies the composition of the intestinal microbiota, altering the metabolite profile of each individual [18]; low-fiber diets, for example, reduce SCFA synthesis, producing harmful metabolites such as lipopolysaccharides (LPS), thus contributing to intestinal dysbiosis [15,19,20].

Dysbiosis involves disturbances in the composition and structure of the gut microbiota resulting in endotoxemia, which is associated with elevated proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), and oxidative stress, triggering systemic inflammation present in CKD [6,20-23].

In CKD, microbiota metabolism is considered a non-traditional but modifiable risk factor influencing the progression of renal damage [24]; dysbiosis disrupts the kidney-gut axis, is linked to increased production of UT, combined with deterioration of renal function, maintains uremic status and results in accelerated decline in GFR [24].

Altered microbiota in CKD

Patients with CKD exhibit gut biochemical changes due to decreased fiber intake, frequent use of antibiotics, and metabolic acidosis [6,25,26]; in addition, elevated uremia increases their flow into the gastrointestinal tract, where urease-expressing bacteria metabolize it into CO2 and ammonia, damaging the epithelial barrier, triggering the immune system response and resulting in dysbiosis, as shown in Figure 1 [7,27-29].

Evidence supports quantitative and qualitative alterations of the microbiota in CKD [16,23,30,31]; renal patients' microbiota has fewer families of *Lactobaci laceae* and *Prevotellaceae*, and of SCFA-producing bacteria, especially butyrate, that protect against inflammation [32], and 100-fold more species of *Enterobacteriaceae* and *Enterococci* [6,23]. Systematic reviews support the findings of changes in the microbiota during CKD, showing an abundance of proteolytic bacteria that produce toxic metabolites, such as the phylum *Proteobacteria* and *Fusobacteria*, the genus *Escherichia/Shigella*, and a lower abundance of *Roseburia*, *Faecalibacterium*, *Pyramidobacter*, *Prevotellaceae* and *Prevotella* [23,33].

A study identified that CKD patients have a lower abundance of *Actinobacteria* and a higher amount of *Verrucomicrobia* compared to healthy subjects, although the role of this change in CKD is unclear [23]. Other research concluded that end-stage disease is characterized by a decrease in the number of

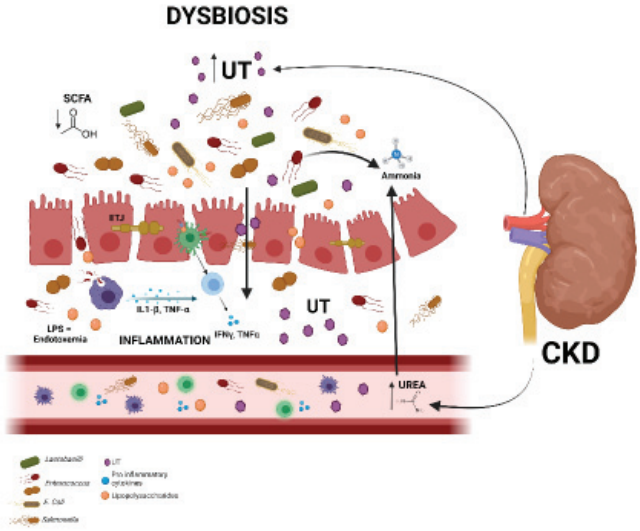

Figure 1: Microbiota alterations in CKD patients.

Bacteroides and an increase in the amount of *Escherichia* and *Shigella* [25], Also, other investigations report that microbiota contains a considerable number of bacterial families with urease, uricase, and tryptophanase activity, and increase of *Escherichia/Shigella*, *Subdoligranulum*, *Fusobacterium* in stage 5 of the disease [2,32].

Such alterations induce structural changes that affect intestinal epithelium, tight junctions and increase gut permeability, thus facilitating the leakage of bacterial metabolites into circulation and triggering immune responses, setting up an inflammatory microenvironment that accelerates the progression of CKD [6,7,27,34,35]. Dysbiosis induces proliferation and abnormal differentiation of B and T lymphocytes, resulting in the production of auto-antibodies and inflammatory molecules, also activates the renin-angiotensin system, along with increased UT production, contributing to the deterioration of renal function [33]. In CKD patients, dysbiosis is involved in establishing end-stage Protein-Energy Wasting (PEW) [35], and it is a determinant factor in altering neuroendocrine-immunological communication mechanisms in kidney disease [33].

Uremic Toxins (UT)

Renal function decline and uncompleted clearance of nitrogen compounds result in UT accumulation [36-38]. Several UTs are generated in the gut, as by-products of amino acid degradation by intestinal bacteria [37]; and they are associated with increased risk of CVD [2,26,30,34]. They include p-cresyl (pC), p-cresyl sulfate (pCS), p-cresyl glucuronide (PCG), indoxyl sulfate (IS), indole-3-acetic acid (IAA), and trimethylamine N-oxide (TMAO).

Evidence supports that serum IS concentration is predictive of CKD progression [39], and that pCS correlates negatively with GFR [40]. A study in hemodialysis patients identified that inflammatory markers, such as IL-6, are correlated to serum IS levels [2]; Yeh et al. in 2016 reported that IS and pCS activate

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inflammatory pathways that accelerate renal damage and increase cardiovascular risk [41]. Other studies have concluded that these UTs are determinants of increased expression of inflammatory markers, and increased oxidative stress, which enhances endothelial dysfunction and progression of CKD [32,34].

We now describe the different action mechanisms of each UT:

p-cresyl (pC) and p-cresyl sulfate (pCS): UT p-cresyl (pC) is a uremic toxin that binds to albumin for excretion by glomerular filtration [42], has a low molecular weight (MW: 108. 14 g / mol); it is synthesized from the catabolism of tyrosine and phenylalanine and is metabolized in the gut microbiota to its conjugates p-cresyl sulfate (pCS) and p-cresyl glucuronidate (pCG) [43]. Heir serum concentration is associated with GFR [44]. In the early stages of CKD, levels increase to 20.1 mg/L, and in the terminal stage, they reach 40.7 mg/L, with concentrations up to 17 times higher than in healthy subjects [42].

Their metabolites have been associated with immune system dysfunctions [45-48]. Evidence *in vitro* found that pCS suppresses STAT5 signaling and significantly reduces peripheral B cells [46], represses certain functions in innate immune system cells, decreases IL-12 synthesis, and increases IL-10 synthesis in peritoneal macrophages [47]. Another research reported that pCS interferes with antigen presentation by decreasing HLD-DR expression, reducing the adaptive immune response [48].

pCS is associated with cardiovascular damage and all its causes of mortality in CKD patients [43,49] due to the proinflammatory effect [12,50,51]. It is implicated in the formation of free radicals produced by leukocytes, endothelial cells, vascular smooth muscle cells, and renal tubular cells, and in the reduction of glutathione levels [52]. *In vivo* research reports certain mechanisms of damage of this UT, it causes mitochondrial damage by inducing AMPK-mediated mitochondrial hyperfusion [53]. Intervenes in endothelial dysfunction by correlating negatively with thrombospondin desintegrina metalloproteinase (ADAMTS) activity and positively with the markers of endothelial activation/damage ANGPT2 and MMP-7 [13]. An experiment in the cell model identified that it induced osteogenesis by triggering pERK / pJNK / pP38 MAPK signaling pathways and NF-κB translocation, which results in uremic vascular calcification [54].

Indoxyl sulfate (IS) and indole-3-acetic acid (IAA): In the colon, intestinal bacteria break down tryptophan into indole-3-acetic acid (IAA) and indole [55]; indole then enters portal circulation and the liver to be hydroxylated by cytochrome P450 2E1 (CYP2E1), then is sulfated by sulfotransferase 1A1 (SULT1A1) to produce indoxyl sulfate (IS) [37]. The evidence suggests that accumulation of these UTs in CKD is associated with a decline in renal function and a worse prognosis [55]. IS plasma levels in CKD patients are 54 higher than in healthy subjects [45]. IS favors dysbiosis by downregulating tight junction-expressing proteins, such as occludin and claudin-1; moreover, it favors oxidative stress-producing free radicals [2].

Several studies correlate these UT to increased cardiovascular risk [2,56]; certain evidence in CKD patients associate IS with adverse cardiovascular events independently of renal function [57], while others report an increased risk of mortality in CKD, but no increased risk of cardiovascular events [43]. Evidence *in vitro* identifies that IS promotes vascular smooth muscle cell (VSMC) proliferation and increases extracellular matrix (ECM) production and deposition, thus inducing calcifications [14], an additional investigation suggests that IS induces a macrophage-mediated inflammation which blocks cholesterol passage to high-density lipoproteins (HDL) [14]. It is also reported that it induces oxidative stress in endothelial cells [45]. An experimental study in rats showed that exposure to IS induces arterial thrombosis by decreasing aortic levels of sirtuin 1, a class III histone deacetylase involved in oxidative stress [58]. However, evidence in humans is limited [57].

They are also implicated in fibrosis mechanisms [12]; the aryl hydrocarbon receptor (AhR) recognizes IS or IAA and triggers signaling pathways activating nuclear factor kappa light chain enhancer of activated B cells (NFkB) and the expression of adhesion molecules; in addition, it induces the production of ROS activating p38 and p42 / p44 mitogen-activated protein kinases (MAPKs), promoting liberation of proinflammatory and profibrotic cytokines, such as transforming growth factor beta (TGF-β) and alpha-smooth muscle actin (α-sma) [2,14]. IS has also been associated with an increase in IL-6 [12].

Trimethylamine N-oxide (TMAO): Trimethylamine N-oxide (TMAO) is a low-molecular-weight metabolite (75 Da) derived from the metabolism of choline, carnitine, and betaine by intestinal bacteria; its synthesis involves two steps: release by gut microbiota from dietary Trimethylamine (TMA) precursors, actively absorbed into the bloodstream for oxidation to TMAO by the liver enzyme monooxygenase. Subsequently, TMAO and TMA can convert to dimethylamine (DMA) [59-62]. The elimination occurs via urine by glomerular filtration [61]. Consumption of foods such as meat, eggs, dairy products, and saltwater fish which are dietary sources of TMAO may influence its serum concentration as well as its metabolic precursors [60], however, the composition of gut microbiota is the main factor that regulates circulating TMAO concentration, along with BMF enzymatic activity and renal function [60,61].

The serum levels of TMAO increase as renal function decreases [61,62]. Various papers documented an increase in TMAO in CKD, with participation in renal fibrosis [37]. Hsu et al. in 2020 reported that stage 2-4 CKD children presented higher serum levels of DMA, TMA, and TMAO than in stage 1, whereas urinary levels of DMA and TMAO in advanced stages were lower [59]. Missailidis et al. reported that patients in stage 5 CKD had a 13-fold increase in TMAO levels compared to controls, and in stages 3-4 TMAO levels were inversely correlated with GFR [60]; Pelletier in 2019 confirmed increased TMAO in hemodialysis patients [61].

High levels of TMAO in CKD are associated with increased cardiovascular risk and it is an independent predictor of mortality in stages 3-5 [2,60], evidence shows that elevated serum TMAO levels in CKD patients are associated with a 70%

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higher risk of mortality [63]. Animal studies have reported that this UT enhances systemic inflammation through macrophage activation and foam cell formation; it is also involved in proatherogenic mechanisms, including disruption of cholesterol transport and platelet response, promoting thrombosis [60,62]. Zhang et al. reported in 2021 that mice fed choline and TMAO increased phosphorylation of SMAD family member 3 (Smad3) in the kidney, an important regulator of the TGF-β signaling pathway in fibrotic kidney disease [62].

Supplementation of prebiotics and probiotics in CKD

Manipulation of the gut microbiome in CKD patients by supplementation with probiotics, prebiotics, or synbiotics has the target to reduce the synthesis and accumulation of UT, and to increase SCFA synthesis, to reduce disease progression [64]. Studies have been conducted on the use of probiotics, mainly *Lactobacillus* and *Bifidobacteria*, as well as prebiotics in CKD, aimed at reversing intestinal dysbiosis [2], to increase SCFA concentration, as butyrate, which has protective effects maintaining intracellular intestinal pH, improving the composition of the gut microbiota [2]; and decreasing oxidative stress, systemic inflammation, and UT production [65].

Prebiotics are non-host-digestible food components that selectively induce the growth or activity of a limited number of intestinal microorganisms that contribute to well-being [6,66]. The main prebiotics are inulin, fructooligosaccharides, galactooligosaccharides, soy oligosaccharides, xylooligosaccharides, and pyrodextrins [6]. Although the impact on the intestinal microbiota of prebiotic treatment has not been investigated by omics sciences [66], they appear to be a strategy within nutritional treatment to regulate the fermentable carbohydrate-protein balance in the colon [26]; here is evidence of their effect on the symptomatology of patients with CKD.

A study conducted in patients with terminal CKD and supplemented with a prebiotic (starch with high corn-resistant amylose content) for 8 weeks concluded that the use of this prebiotic decreases intestinal inflammation and oxidative stress [34]. Likewise, Sirich et al. supplemented patients on hemodialysis therapy with this type of resistant starch for 6 weeks and found a significant reduction in IS and pC [67]; another investigation, also in patients on replacement therapy using the same type of supplement, reported decreased levels of total and LDL cholesterol, and inflammatory markers: TNF-α, IL-6, IL-8 and C-reactive protein (pCr) [68].

Other types of prebiotics studied for the reduction of UT, are oat and barley beta-glucans; a study performed with healthy subjects supplemented with this class of prebiotics identified that the serum level of pCS decreases, while the level of IS remains unchanged [21]. A 3-month, double-blind, randomized, controlled trial supplemented patients with end-stage CKD with 12 g of short-chain fructoligosaccharide (FOS)-type prebiotics, with no significant reduction in serum or urinary levels of pCS, IS, or IAA, markers of intestinal permeability such as zonulin: or markers of inflammation IL-6 and pCr [26].

Probiotics are live microorganisms that are beneficial to host health in adequate amounts [19,65]. Some of their functions include increasing the fermentation of dietary fiber, reducing intestinal pH, decreasing uremia by degrading urea and uric acid, and modulating the composition of the intestinal microbiota [65]. Evidence suggests that the gut microbiota of CKD patients receiving probiotic supplementation utilizes metabolic waste as a substrate, leading to a decrease in toxic metabolites [65]. There are contradictory results on the effect of probiotics on the composition of the microbiota: in some studies, an increase in the proportion of genera with no effect on the composition and diversity of the gut microbiota has been observed, while in others changes in its composition have been observed [19].

Evidence suggests that probiotics positively affect the immune system, generating increased expression of anti-inflammatory cytokines, such as IL-10, and decreased expression of proinflammatory cytokines, such as IL-6 and TNFα [65]. Studies with probiotic supplementation in CKD patients reported encouraging results against uremia and inflammation, although long-term studies are needed [27]. SYNERGY (Symbiotics alleviating renal failure by improving gut microbiology) is one of the first trials in this field, no changes in GFR or proinflammatory markers were found, but changes in the nutritional status of patients were observed by increasing serum albumin levels and slowing the progression of proteinuria, as well as significant increases of Bifidobacterium in the composition of the microbiota [69].

A randomized clinical trial administering a probiotic supplement containing 16 × 109 CFU/day of L. casei shirota to patients with stage 3-4 CKD for two months, reported a decrease in serum urea levels; similar results were observed in a pilot study using different bacterial strains (*L. acidophilus*, *B. longum* and *S. thermophilus*) were used at doses of 9 × 109 CFU/day for three months, finding a reduction in urea nitrogen levels; meanwhile, a placebo-controlled clinical trial with oral administration of B. longum capsules to HD patients reported a reduction in serum phosphorus concentration [65]. Meanwhile, an animal model study reported that treatment with 1 x 10 CFU/kg/day of Lactobacillus increases urinary protein excretion [70].

The identification of bacterial strains or intermediate metabolites as therapeutic targets to modulate altered gut microbiota could be a target in the treatment of CKD [6,19]. Modulation of the gut microbiota by prebiotics and probiotics provides an attractive approach in CKD with interesting findings in animal models for the reduction of UT and intestinal permeability [24,70,71].

Conclusion

Uremic toxins accumulated as a result of impaired renal function modulate pathways of oxidative stress, systemic inflammation, and dysbiosis in the context of CKD, so the study of their pathophysiological mechanisms is important to better understand their role in CKD progression.

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Restoration of the gut microbiota in CKD patients by prebiotic and probiotic supplementation is an alternative treatment but requires further research and evaluation to identify the type of prebiotic or useful bacterial strains, dose, and duration of treatment for beneficial effects in CKD patients.

Author contributions

Conceptualization, C.J.D.l.C.-A and S.R.-D.l.S; investigation, C.J.D.l.C.; writing—original draft preparation, C.J.D.l.C.-A and S.R.-D.l.S.; writing—review and editing, C.J.D.l.C.-A and S.R.-D.l.S.; supervision, J.F.T.-R. and S.R.-D.l.S. All authors have read and agreed to the published version of the manuscript.

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